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**(54) PROCEDE POUR ENCAPSULER DES COMPRIMES DANS UNE
CAPSULE; FORME POSOLOGIQUE SOLIDE OBTENUE
GRACE A CE PROCEDE**
**(54) PROCESS FOR ENCAPSULATION OF CAPLETS IN A CAPSULE
AND SOLID DOSAGE FORMS OBTAINABLE BY SUCH
PROCESS**

(57) Procédé pour encapsuler des comprimés sous forme de capsule; formes posologiques solides ainsi obtenues. En particulier, fabrication d'une capsule inviolable renfermant une composition pharmaceutiquement active. Dans une version privilégiée, le comprimé est plus long que les deux moitiés de la coquille capsulaire. Dans cette version, une partie du comprimé demeure exposée après la fabrication de celui-ci.

(57) A process for encapsulation of caplets in a capsule and the solid dosage capsules obtained thereby. In particular, the manufacture of a tamper-proof capsule containing a pharmaceutically active composition. In a preferred embodiment, the caplet is greater in length than both halves of the capsule shell. In this embodiment, part of the caplet remains exposed after the capsule is manufactured.

ABSTRACT

A process for encapsulation of caplets in a capsule and the solid dosage capsules obtained thereby. In particular, the manufacture of a tamper-proof capsule containing a pharmaceutically active composition. In a preferred embodiment, the caplet is greater in length than both halves of the capsule shell. In this embodiment, part of the caplet remains exposed after the capsule is manufactured.

PROCESS FOR ENCAPSULATION OF CAPLETS IN A CAPSULE
AND SOLID DOSAGE FORMS OBTAINABLE BY SUCH PROCESS

Field of the Invention

The present invention relates to a process for encapsulation of caplets in a capsule and to solid dosage forms obtainable by such a process, and more particularly, to the manufacture of a tamper-proof capsule containing a pharmaceutically active composition.

Background of the Invention

Various oral medications have been manufactured in the form of so called caplets, which can be swallowed by patients during their regimen of taking medication. Caplets, however, are not as easily swallowed by patients as capsules having, for example, a gelatin coating. Additionally, capsule coatings are desirable over caplets since the coatings provide a neutral taste in contrast to caplets per se which sometimes contain pharmaceutical substances that taste, for example, bitter. Thus, patients, in particular children, refuse to swallow such caplets per se. Attempts have therefore been made to encapsulate caplets in a capsule by means of a gelatin cover.

U.S. Patent No. 4,867,983 to Berta describes a method for double dipping gelatin coated caplets. The method provides a procedure for coating solid cores, such as caplets, with a first gelatinous coating on one end, and then with a second gelatinous coating on the other end which is thicker than the first, to simulate the interlocking halves of a hollow capsule. The second, thicker gelatinous coating can be provided with a single

5 gelatin coating from a bath having a higher viscosity
than the bath used to provide the first gelatinous
coating. Alternatively, the second gelatinous coating
can be provided by double dipping to provide layers of
10 gelatinous material or gelatin. This known coating is
disadvantageous in that the gelatinous coating and the
color distribution is not uniformly distributed over the
caplets by this process. Moreover, an overlapping of the
different coatings results in color changes of the
15 coatings. Additionally, the dip margins obtained by the
known process tend not to be straight. Furthermore, the
coatings according to the above patent chip off under
stress if the coated caplets are stored under dry
conditions and/or high temperature. Finally, the dip
coating process of U.S. Patent No. 4,867,983 is time
15 consuming and expensive.

20 From U.S. Patent No. 5,081,822 to Boyd et al, an
automatic caplet filler is known for filling normal
gelatin capsules with caplets. The capsules formed by
this automatic caplet filler, however, are
disadvantageous in that they can be easily manipulated.
Sealing of the capsules has to be effected by means of an
additional gelatin strip or by gluing of the caplets in
the capsule with an adhesive, as e.g. described in U.S.
25 Patent No. 4,928,840 or European Patent Application No.
0435726. This further treatment of the capsules may have
the effect that substances other than the medication are
encapsulated in the capsule. If on one hand a
water-based adhesive is used for gluing the capsule
halves together, the capsule as well as the caplet may be
30 deformed. If on the other hand, an adhesive containing an
organic solvent is used, a brittleness of the capsule
will be the result. Finally, if the capsule halves are
connected with each other by means of a heat shrinking

process, a visible gap will remain between the capsule halves.

It is therefore the object of the present invention to provide a method for encapsulating caplets in a capsule in a tamper-proof form. It is yet another object of the invention to provide a cost-effective process for easily manufacturing tamper-proof solid dosage forms. It is yet another object of the present invention to provide a solid dosage form comprising a caplet covered by a capsule. It is yet another object of the present invention to provide a pharmaceutical dosage form having a greater resistance to breaking than known products. A further object of the present invention is to provide a tamper-proof solid dosage form.

15 Summary of the Invention

According to a first aspect, the present invention provides a process for encapsulation of a caplet in a capsule by cold shrinking together capsule parts, which are filled with a caplet. According to another aspect, the present invention provides a solid dosage form obtainable by such a process. The solid dosage form according to the present invention is tamper-proof in that the caplet contained in the capsule cannot be removed from the capsule without destroying same.

25 The process according to the present invention furthermore provides a capsule product comprising several parts, which are combined with each other in a way that no visible slits between the capsule parts are present after the cold shrink procedure. The solid dosage forms of the present invention have a completely smooth surface, so that same can be swallowed easily by patients.

More specifically, a process for encapsulating caplets in a capsule is provided, which comprises the following steps:

- a. providing empty capsule parts,
- 5 b. filling at least one of said capsule parts with one or more caplets,
- c. putting said capsule parts together, and
- d. treating the combined capsule parts by cold shrinking.

10 Moreover, a solid dosage form comprising a caplet and a capsule coating obtainable by such process is described.

Description of Preferred Embodiments of the Invention

15 The capsule shell in which the caplet is to be enclosed preferably comprises two shell halves, a body portion and a cap portion. Other capsules comprising more than two parts are also possible. The capsule is typically a hollow shell of generally cylindrical shape having a diameter and length sufficient so that the 20 caplet fits appropriately in the empty capsule. The clearance of the capsule shell and the caplet is preferably about + 0.5 mm. According to a specifically preferred embodiment of the present invention, the clearance of the capsule shell and the caplet is in the 25 range of from about 0 to about - 0.5 mm, which means that the caplet is compressed in the capsule.

I.1) Moisture content of the capsule shells:

30 A specifically preferred process of the present invention is carried out as follows. Empty capsule parts are either kept after production at humid conditions of 40 to 90 %, particularly 60 to 80 %, relative humidity to retain a moisture content of 14 to 19 %, preferred 15 to 18 % and more preferred 16 to 18 % by weight of the

capsule shell or are re-humidified to said moisture content before feeding into a capsule filling machine.

The first capsule shell part is then kept under humid conditions within the filling machine at said moisture content during rectifying and assembling with a caplet having a moisture content in the range of from about 0 to about 12 % by weight.

A second or further capsule shell part is processed in the same manner as the first one. Finally, the encapsulated dosage form is dried at a relative humidity in the range of from about 20 to about 40 % and a temperature in the range of from about 15 to about 60°C, preferably from about 15 to about 40°C, more preferably from about 18 to about 25°C.

Caplets having a low moisture content of in the range of from about 0 to about 6 % by weight, or more preferably of from about 0 to about 3 % by weight, are especially suitable to be used in the process of the present invention. Conical ends of the caplet make the insertion of the caplet into one half of the capsule easier. After drying and shrinking the capsule parts together, the capsule can be further film coated, which coating may be enteric.

The capsule shell material can be a hydrophilic polymer, gelatin being the preferred choice. Other suitable capsule shell materials include starch, casein, chitosan, soya bean protein, safflower protein, alginates, gellan gum, carrageenan, xanthan gum, phtalated gelatin, succinated gelatin, cellulosephthalate-acetate, polyvinylacetate, hydroxypropyl methylcellulose, polyvinylacetate-phtalate, polymerisates of acrylic or methacrylic esters or

mixtures thereof. The capsule shell material may furthermore contain from about 0 to about 40 % pharmaceutically acceptable plasticizers based upon the weight of the hydrophilic polymer. The plasticizer which may be employed can be selected from polyethylene glycol, glycerol, sorbitol, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propyleneglycol, mono-, di, or tri-acetates of glycerol or mixtures thereof.

10 Additionally, the capsule shell material may contain pharmaceutically acceptable lubricants in the range of from about 0 to about 10 % based upon the weight of the hydrophilic polymer. The lubricant may be selected from aluminiumstearate, calciumstearate, magnesiumstearate, tinstearate, talc, sodium lauryl sulfate, lecithins, mineral oils, stearic acid or silicones or mixtures thereof.

20 Moreover, the capsule shell material may contain pharmaceutically acceptable coloring agents in the range of from about 0 to about 10 % based upon the weight of the hydrophilic polymer. The coloring agent may be selected from azo-quinophthalone-, triphenylmethane-, xanthene-dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Further suitable coloring agents are sunset yellow, allura red, amaranth, cochineal red, azogermanine, tartrazine, brilliant black, canthaxanthin, patent blue, fast green, brilliant blue, acid green, erythrosine, quinoline yellow, indigotine, curcumin or carbon black.

30 Furthermore, the capsule shell material may contain pharmaceutically acceptable extenders in the range of from about 0 to about 95 % based upon the weight of the

hydrophilic polymer. The extender may be selected from sunflower proteins, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, lactose, gum arabic, acrylates or methacrylates, cellulose acetyl phthalates, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulosephthalate, hydroxymethylcellulose, polyvinylpyrrolidone, shellac, bentonite, polyvinyl-acetatephthalate, phthalated gelatin, succinated gelatin, agar agar, hydroxyalkylstarches or mixtures thereof.

The solid pharmaceutical dosage form according to the present invention also may comprise a coating selected from cellulosephate, polyvinyl acetate phthalate, methacrylic acid polymers, hypromellose phthalate, hydroxyalkyl methyl cellulose phthalates or mixtures thereof.

The capsule parts of the solid dosage form of the present invention may have the same or different lengths and/or the same or different color. In the contact area of the capsule parts, the solid dosage form may be banded or easily dividable. The caplet being contained in the capsule can have a preformed step or groove in the dividing position of the capsule. To furthermore improve the caplet which is contained in the capsule, the caplet can be coated with an acceptable coating for tablet processing. In some cases, uncoated caplets are, however, preferred. A better contact between the inner shells of the capsule parts and the caplets can be obtained by treating the inner shells and/or the surface of the caplet with an adhesive. A suitable technique to apply the adhesive is spraying same on the shells and caplets immediately before assembling same. Suitable adhesives are e.g. tackidex or an aqueous gelatin solution.

II. Capsule shell halves cover not completely the caplet:

A further aspect of the invention is to provide encapsulated dosage forms in which the capsule shell halves do not completely cover the whole caplet, which means the caplet is longer than the two combined shell halves. This will provide capsules with additional advantageous features. If each of the capsule halves have a different color and the caplet has a third color, a three-colored capsule will be obtained, or, if the shell halves have the same color and the caplet has a different color, a color banded capsule will be obtained. A second optional feature may be obtained by use of enteric coated capsule shell halves. In such a case a capsule with delayed release will be obtained, releasing the medicament in the stomach first from the small release band between the shell halves and later on from the capsule openings.

III. Global concept of moisture control:

A further aspect of the invention is use of the described moisture control and rehumidification on common encapsulation machines with all kinds of common hard gelatin capsule types. The inventive process gives much better filling results especially with filling machines in hot and dry areas for the encapsulation of all kinds of fillings like powders, pellets, liquids, microcapsules, tablets etc. The preferred process in this case is carried out as follows. Empty capsule bodies and caps preferred assembled in a pre-lock state are either kept after production at humid conditions of 40 to 90 %, particularly 60 to 80 %, relative humidity to retain a moisture content of 14 to 19 %, preferred 15 to 18 % and more preferred 16 to 18 % by weight of the capsule shell or are re-humidified to said moisture before opening and sorting in the capsule filling machine. Capsule bodies are then kept under humid

conditions within the filling machine at said moisture content during rectifying and filling with the desired product. In the same way the capsule caps are kept at moisture content during rectifying and finally assembling with the filled capsule bodies. Finally, the capsule is dried at 20 to 40 % relative humidity and 15 to 60°C, preferably 15 to 40°C, more preferably 18 to 25°C.

The solid dosage form according to the present invention may, for example, comprise a pharmaceutically or agrochemically active composition. Furthermore comprised in the solid dosage form can, for example, be a foodstuff or a dyestuff composition. In case the solid dosage form of the present invention contains a pharmaceutical composition, the active substance of same can, for example, be selected from betamethason, thioctacid, sotalol, salbutamol, norfenefrin, silymarin, dihydergotamin, buflomedil, etofibrat, indometacin, oxazepam, acetyldigoxin, piroxicam, haloperidol, isosorbide mononitrate, amitriptylin, diclofenac, nifedipin, verapamil, pyritinol, nitrendipin, doxycyclin, bromhexin, methylprednisolon, clonidin, fenofibrat, allopurinol, pirenzepin, levothyroxin, tamoxifen, metildigoxin, o-(β -hydroxyethyl)-rutoside, propicillin, aciclovirmononitrat, paracetamol, naftidrofuryl, pentoxifyllin, propafenon, acebutolol, l-thyroxin, tramadol, bromocriptin, loperamid, ketotifen, fenoterol, ca-dobelisat, propranolol, minocyclin, nicergolin, ambroxol, metoprolol, β -sitosterin, enalaprilhydrogenmaleate, bezafibrat, isosorbide dinitrate, gallopamil, xantinolnicotinat, digitoxin, flunitrazepam, bencyclan, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylenicillin, furosemid, bromazepam, flunarizin, erythromycin, metoclopramid, acemetacin, ranitidin, biperiden, metamizol, doxepin, dipotassium-chlorazepat, tetrazepam,

estramustinphosphate, terbutalin, captopril, maprotilin,
 prazosin, atenolol, glibenclamid, cefaclor, etilefrin,
 cimetidin, theophyllin, hydromorphon, ibuprofen,
 primidon, clobazam, oxaceprol, medroxypregesteron,
 5 flecainid, Mg-pyridoxal-5-phosphateglutamate,
 hymechromon, etofyllinclofibrat, vincamin, cinnarizin,
 diazepam, ketoprofen, flupentixol, molsidomin,
 glibornurid, dimetinden, melperon, soquinolol,
 dihydrocodein, clomethiazol, clemastin, glisoxepid,
 10 kallidinogenase, oxyfedrin, baclofen,
 carboxymethylcystsin, thioridacin, betahistin,
 1-tryptophan, myrtol, bromelaine, prenylamin,
 salazosulfapyridin, astemizol, sulpirid, benzerazid,
 dibenzepin, acetylsalicylic acid, miconazol, nystatin,
 15 ketoconazol, sodium picosulfate, colestyramin,
 gemfibrocil, rifampicin, fluorcortolon, mexiletin,
 amoxicillin, terfenadrin, mucopolysaccharidpolysulfuric
 acid, triazolam, mianserin, tiaprofensaure,
 amenziniummetilsulfate, mefloquin, probucol, quinidine,
 20 carbamazepin, Mg-1-aspartate, penbutolol, piretanid,
 amitriptylin, caproteron, sodium valproinate, mebeverin,
 bisacodyl, 5-amino-salicyclic acid, dihydralazin,
 magaldrat, phenprocoumon, amantadin, naproxen, carteolol,
 famotidin, methyldopa, auranofin, estriol, nadolol,
 25 levomepromazin, doxorubicin, medofenoat, azathioprin,
 flutamid, norfloxacin, fendilin, prajmaliumbitartrate,
 aescin, acromycin, anipamil, benzocain, β -carotin,
 cloramphenicol, chlorodiazepoxid, chlormadinonacetat,
 clorothiazid, cinnarizin, clonazepam, codein,
 30 dexamethason, dicumarol, digoxin, drotaverin, gramicidin,
 griseofulvin, hexobarbital hydrochlorothiazide,
 hydrocortison, hydroflumethiazid, ketoproten, lonetil,
 medazepam, mefrusid, methandrostenolon, sulfaperin,
 nalidixic acid, nitrazepam, nitrofurantoin, estradiol,
 35 papaverin, phenacetin, phenobarbital, phenylbutazon,
 phenytoin, prednison, reserpine, spironolacton,

streptomycin, sulfamethazin, sulfamethizol,
sulfamethoxazol, sulfamethoxydiazin, sulfathiazol,
sulfisoxazol, testosteron, tolazamid, tolbutamid,
trimethoprim, tyrothricin or mixtures thereof.

5 The purpose of the above description is to
illustrate some configurations and uses of the present
invention, without implying any limitation. It will be
apparent to those skilled in the art that various
modifications and variations may be made in the process
10 and product of the invention without departing from the
spirit or scope of the invention.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for encapsulation of caplets in a capsule, comprising the following steps:

a. providing empty first and second capsule shell parts,

b. filling at least one of said capsule parts with one or more caplets

c. putting said capsule parts together, and

d. treating the combined capsule parts by cold shrinking,

wherein said empty capsule parts are either kept after production at humid conditions of 40 to 90 % relative humidity to retain a moisture content of 14 to 19 %, preferred 15 to 18 % and more preferred 16 to 18 % by weight of the capsule shell or are re-humidified to said moisture content before feeding into a capsule filling machine,

wherein a first capsule shell is kept under humid conditions within the filling machine at said moisture content during rectifying and assembling with a caplet having a moisture content of 0 to 12 % by weight,

wherein a second capsule shell is processed in the same manner, and

wherein the encapsulated dosage form is dried at 20 to 40 % relative humidity and 15 to 60°C.

2. The process of Claim 1 wherein the encapsulated dosage form is dried at a temperature of 15 to 40°C.

3. The process of Claim 1 wherein the encapsulated dosage form is dried at a temperature of 18 to 25°C.

JJ:vs

4. A capsule comprising first and second capsule shell parts which have been cold shrunk about a caplet wherein said shell parts have a moisture content in the range of 14 to 19 % by weight; wherein said caplet has a moisture content in the range of 0 to 12 % by weight; wherein said capsule is film coated with an enteric film; and wherein said shell parts do not completely cover said caplet.
5. The capsule of Claim 4 wherein each of the shell parts and the caplet are a different color.
6. The capsule of Claim 4 wherein the shell parts are both a first color and the caplet is a second color wherein the first color and the second color are different.